

Exhibit 15

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Immediate adverse events after second trimester medical termination of pregnancy: results of a nationwide registry study

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BACKGROUND: Increasing gestational age is associated with an increased risk of complications in studies assessing surgical termination of pregnancy (TOP). Medical TOP is widely used during the second trimester and little is known about the frequency of complications. This epidemiological study was undertaken to assess the frequency of adverse events following the second trimester medical TOP and to compare it with that after first trimester medical TOP.

METHODS: This register-based cohort study covered 18 248 women who underwent medical TOP in Finland between 1 January 2003 and 31 December 2006. The women were identified from the Abortion Registry. Adverse events related to medical TOP within 6 weeks were obtained from the Hospital Discharge Registry.

RESULTS: When compared with first trimester medical TOP, second trimester medical TOP increased the risk of surgical evacuation [Adj. odds ratio (OR) 7.8; 95% confidence interval (CI) 6.8–8.9], especially immediately after fetal expulsion (Adj. OR 15.2; 95% CI 12.8–18.0). The risk of infection was also elevated (Adj. OR 2.1; 95% CI 1.5–2.9). Within the second trimester, increased length of gestation did not influence the risk of surgical evacuation or infection after medical TOP.

CONCLUSIONS: Medical TOP during the second trimester is generally safe. Surgical evacuation of the uterus is avoided in about two-thirds of cases, though it is much more common than after first trimester medical TOP. The risks of surgical evacuation and infection do not increase with gestational weeks in the second trimester TOP.

Key words: complication / adverse event / second trimester / termination of pregnancy / medical

Introduction

With an estimated 29 induced abortions per 1000 women aged 15–44 years globally per annum (Sedgh *et al.*, 2007), termination of an unwanted pregnancy is one of the most common gynaecological procedures. In developed countries, legal termination of pregnancy (TOP) is safe (Sedgh *et al.*, 2007), the overall death rate being 10 per 100 000 procedures (Guttmacher Institute, 2009).

While the overall risks are low, increasing gestational age is, nevertheless, associated with an increased risk of complications. For example, from 1988 to 1997 in USA the risk of death increased by 38% for each additional week of gestation (Bartlett *et al.*, 2004).

However, these data are mostly derived from surgical abortion (Guttmacher Institute, 2009). In large studies medical TOP using the combination of mifepristone and misoprostol seems to be more effective in earlier gestation (Ashok *et al.*, 2002, 2004). Up to 9 weeks of gestation the overall rate of complete abortion can be up to 98% with only 2% needing a surgical intervention (Ashok *et al.*, 2002). At 13–21 weeks of gestation the rate of successful abortion has been reported to be as high as 97%, with only 8% needing a surgical intervention (Ashok *et al.*, 2004).

The method of second trimester TOP is still controversial, especially regarding adverse events and complications. Yet studies comparing surgical and medical second trimester TOP are rare and

randomized comparison has proven difficult to carry out (Grimes, 2008; Lohr et al., 2008). In Northern Europe second trimester TOP is largely performed medically, i.e. using a combination of mifepristone and misoprostol (Lohr et al., 2008). Therefore there is a need for an epidemiological study evaluating the effects following the second trimester medical TOP.

The purpose of the present study was to assess the rate of adverse events and complications following the second trimester medical TOP and to compare it with those following the first trimester medical TOP. We focused in particular on haemorrhage, infection and surgical evacuation in cases of incomplete abortion.

Materials and Methods

We performed a register-based cohort study which included women who underwent medical TOP in Finland between 1 January 2003 and 31 December 2006. We linked three national registries: the study cohort was identified from the Abortion Registry (THL, 2010a) and data on adverse events were obtained from the Hospital Discharge Registry (THL, 2010b) (official name: Care Registry for Health Care Institutions) and the Cause-of-Death Registry of Statistics Finland (Statistic Finland, 2010).

The flow chart (Fig. 1) shows the formation of the cohorts. When a woman had more than one induced abortion during the study period, only the first TOP was included. Altogether, 695 (3.5%) women who underwent medical TOP were excluded from the study. The exclusion criteria were:

- (i) Any other concomitant surgical procedure (laparoscopic sterilization, $n = 20$) performed at the same time.
- (ii) Data could not be linked to hospital registry ($n = 668$), i.e. TOP performed at a private clinic as outpatient care.
- (iii) Other reasons ($n = 7$): one woman with a kidney transplant and immunosuppressive medication, five women with twin pregnancies and one woman with previously diagnosed uterus bicornis.

Data concerning the method of induced abortion was derived from linkage of the Abortion Registry (THL, 2010a) and the Hospital Discharge Registry (THL, 2010b). During 2003–2006 medical TOP was defined in the Abortion Registry as: use of mifepristone alone or in combination with misoprostol or other prostaglandins, or prostaglandins alone. Details of the medical methods used were not available. However, mifepristone became available in Finland in 2000. Finnish national guidelines on TOP were published 25 September 2001 (Finnish Medical Society Duodecim, 2007). This guideline recommends a medical abortion regimen of 200 mg mifepristone orally followed by vaginal administration of 0.4–0.8 mg misoprostol. For second trimester TOP, the procedure is performed in a hospital setting and misoprostol doses (0.4 mg) are repeated every 3–4 h up to five times per day until abortion. Routine sonographic evaluation is not recommended following abortion. The decision to perform surgical evacuation is made on clinical grounds, i.e. in cases of heavy bleeding or retained placenta. Taking this into consideration, the years 2003–2006 were selected for analysis as to the best of our knowledge during this time period the medical TOP at all durations of gestation were performed using the combination of mifepristone and misoprostol throughout Finland.

Participants were divided into two groups according to the weeks of gestation at the time of TOP. First trimester was defined as gestational weeks up to 12 (84 days of amenorrhea) and second trimester as gestational weeks 13–24 (85–168 days of amenorrhea). This division was derived from Finnish legislation on induced abortion (FINLEX, 1970) as

well as from national guidelines on TOP (Finnish Medical Society Duodecim, 2007). Data on background characteristics (age, previous pregnancies, socioeconomic and marital status, duration of gestation, year, indication for TOP, place of residence) were identified from the Abortion Registry (THL, 2010a). Women undergoing TOP for fetal indications, i.e. suspected or confirmed fetal anomalies or abnormalities (12 women, i.e. 0.07% during the first trimester and 844 women, i.e. 42% during the second trimester) were excluded. The final diagnosis of the fetal indication was not available and as the effect of fetal abnormalities on the adverse events or complications could not be assessed these pregnancies were excluded from the study analysis.

TOP is allowed in Finland up to 20 weeks of gestation (140 days of amenorrhea) or up to 24 weeks of gestation (168 days of amenorrhea) in cases of a confirmed medical condition of the fetus (FINLEX, 1970). Approval with a legal indication for TOP is needed, though the legislation is interpreted liberally. The indications can be grouped as medical (women's or fetal health), ethical (e.g. rape) and social reasons. Social reasons include pregnancy and childbirth being an unbearable burden to a woman, age under 17 or over 40 years, and 4 or more deliveries. The approval for TOP has to be applied for from The National Supervisory Authority for Welfare and Health (Valvira, 2010) for all terminations because of congenital anomalies or if gestational weeks are over 12.

The follow-up time after TOP was 6 weeks (42 days). From the registries described above, we retrieved information on the diagnoses, based on ICD-10, the International Statistical Classification of Disease (2010) and operation codes based on the Nordic Classification of Surgical Procedures (2010) concerning all hospital-inpatient episodes (all hospitals) and outpatient visits (all public hospitals) within the follow-up period. Diagnoses and codes were evaluated to select those considered to be of clinical importance and related to TOP.

Complications were divided into following outcomes:

- (i) Haemorrhage (any reported haemorrhages).
- (ii) Infection (pelvic inflammatory disease, endometritis, cervicitis, wound infections, pyrexia of unknown origin, urinary tract infections and septicemia).
- (iii) Incomplete abortion (surgical evacuations or any reported incomplete abortion). Surgical evacuation was divided into three outcomes: total (all patients undergoing evacuation), evacuation at the time of TOP (i.e. following fetal expulsion and during the first stay at the hospital) and evacuation during follow-up (i.e. after the first hospital stay).

Some rare complications were considered as severe complications. They were:

- (i) Injuries or other reasons for surgical procedures (all injuries, cervical laceration, uterine perforation, all surgical interventions during the time of follow-up).
- (ii) Thromboembolic disease (pulmonary embolism, deep vein thrombosis).
- (iii) Death (death from any cause, pregnancy-related death according to the World Health Organization definition).

This classification was based on that reported in the Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists (Davies et al., 2004) and further modified for our study.

This study was approved by the Ministry of Social Affairs and Health as required for registry-based studies in Finland. Statistics Finland also gave their permission to use confidential personal-level data from the death registry. The Data Protection Ombudsman was notified regarding data linkage before the analyses, as required by the national data-protection legislation.

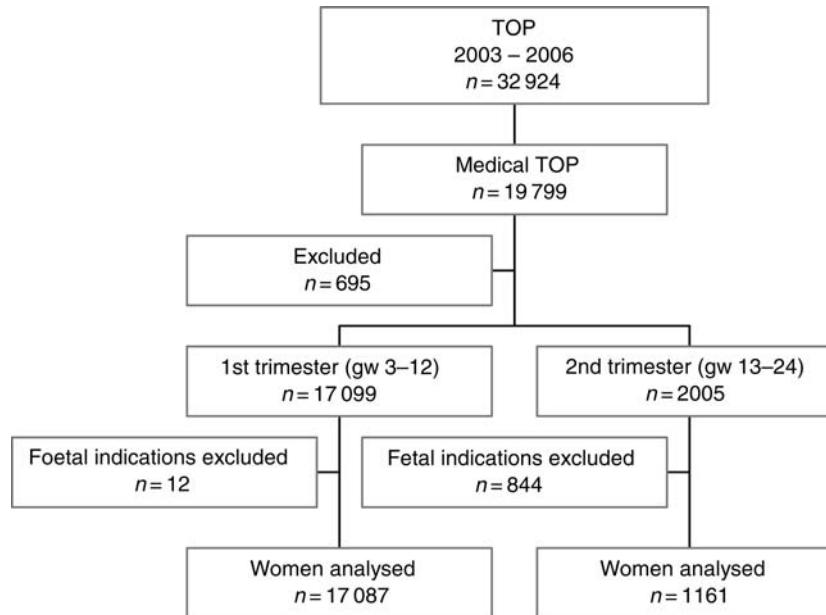


Figure 1 Flow chart detailing the study cohorts. Gw, gestational weeks.

All personal-level data that could be used to identify individuals was removed before the actual analysis was started.

Statistical analysis

Statistical analyses were performed using Predictive Analysis Software (PASW) 18.0 for Mac (SPSS Inc., Chicago, IL, USA). Differences in continuous variables were analysed with Mann–Whitney *U*-test for skewed data and data were presented as median and interquartile range (IQR). The χ^2 test or Fisher's exact test were used as appropriate for independent nominal data. The level of statistical significance was $P < 0.05$. In the analysis of surgical evacuation percentages during the observed time, 95% confidence interval (CI) for percentage was presented. Binary logistic regression models were used to adjust for differences in the background characteristics in comparison of the first and second trimester TOP. The background characteristics that differed statistically significantly between the groups were entered in the analysis. Estimated risks are presented as odds ratios (OR) with 95% CIs.

Results

The observed cohort consisted of 18 248 women who underwent medical TOP between 2003 and 2006, 94% during the first trimester and 6% during the second trimester. During that period 57 and 95% of all terminations of pregnancy were performed medically in the first and second trimester, respectively.

The duration of gestation [median (IQR)] was 7 weeks (7–8) during the first trimester and 15 weeks (14–17) during the second trimester. Table 1 shows the demographics of the study groups. Compared with the first trimester cohort, women undergoing medical TOP during the second trimester were younger, more often single or cohabiting and less often married. They were also more often of lower socioeconomic status and had had fewer previous deliveries. In the second trimester, the indication for medical TOP was more often age under 17

years, unknown or due to woman's health issues and less often social (i.e. continuation of pregnancy, and subsequent childbirth forming an unbearable burden to the woman) than for the first trimester medical TOP.

The main adverse events and complications (haemorrhage, infection, incomplete abortion, i.e. of the requirement for surgical evacuation) are shown in Table II. Medical second trimester TOP increased the risk of surgical evacuation, especially immediately after expulsion of the fetus when compared with the first trimester medical TOP. Second trimester medical TOP was also associated with a higher risk of infection. The risk of haemorrhage was lower during and after second trimester TOP, except in cases when surgical evacuation of residual tissue was needed.

Medical TOP was followed by 23 (0.13%) surgical procedures other than evacuation, i.e. severe complications. Of these, 20 (0.12%) occurred after first trimester medical TOP and 3 (0.26%) after second trimester medical TOP ($P < 0.2$). First trimester medical TOP was followed by a laparoscopic saturation of the uterus in three cases and 17 other repairing operations and second trimester medical TOP was followed by one abdominal hysterectomy, one saturation of the cervix and one other repair operation. There were no thromboembolic diseases during follow-up. There were no deaths as a result of TOP during the study period.

The effect of increasing gestation on the surgical evacuation, infection and haemorrhage was evaluated. The overall incidence of surgical evacuation following medical TOP was 9.9% (95% CI 9.5–10.3). The percentages of surgical evacuation compared with increasing gestation are shown in Fig. 2. The need for surgical evacuation increased as gestational weeks increased beyond 11. The overall incidence of infection following medical TOP was 2.1% (95% CI 0.8–3.9). The percentages of infection compared with increasing gestation are shown in Fig. 3. The risk of infection increased with increasing gestation. The

Table 1 Demographics of the women undergoing medical TOP in 2003–2006.

	First trimester (n = 17087)	Second trimester (n = 1161)	P-value
Age (years)	25 (20–32)	22 (18–30)	<0.001
Marital status			
Married	3235 (18.9)	119 (10.2)	<0.001
Cohabiting	2843 (16.6)	222 (19.1)	0.03
Single	11009 (64.4)	820 (70.6)	<0.001
Residence			
Urban	12379 (72.4)	853 (73.5)	0.5
Densely populated	2494 (14.6)	155 (13.4)	0.2
Rural	2214 (13.0)	153 (13.2)	0.8
Socioeconomic status			
Upper white-collar workers	1010 (5.9)	27 (2.3)	<0.001
Lower white-collar workers	3299 (19.3)	159 (13.7)	<0.001
Blue-collar workers	2214 (13.0)	148 (12.7)	0.8
Students	5895 (34.5)	400 (34.5)	0.97
Others	1086 (6.4)	80 (6.9)	0.5
Unknown	3583 (21.0)	347 (29.9)	<0.001
Previous deliveries	7478 (43.8)	416 (35.8)	<0.001
Previous miscarriage	2164 (12.7)	152 (13.1)	0.7
Previous TOP	2664 (15.6)	184 (15.8)	0.8
Current TOP			
Year of TOP			
2003	3691 (21.6)	265 (22.8)	0.3
2004	4270 (25.0)	314 (27.0)	0.1
2005	4553 (26.6.)	295 (25.4)	0.4
2006	4573 (26.8)	287 (24.7)	0.1
Indication for TOP			
Woman's health	46 (0.3)	13 (1.1)	<0.001
Social	15317 (89.6)	914 (78.7)	<0.001
Ethical	6 (<0.1)	0	0.7
Age < 17	1035 (6.1)	160 (13.8)	<0.001
Age ≥ 40	417 (2.4)	27 (2.3)	0.8
≥4 deliveries	219 (1.3)	18 (1.6)	0.4
Unknown	47 (0.3)	29 (2.5)	<0.001

Data shown as numbers (percentages) or median (IQR, interquartile range).

overall incidence of haemorrhage following medical TOP was 16.9% (95% CI 15.6–18.2). The risk of haemorrhage varied according to gestation.

Discussion

We found that in comparison with the first trimester medical TOP, second trimester medical TOP was associated with an increased risk of surgical evacuation and infection. However, serious complications that need surgical repair after medical TOP and medical second trimester TOP were rare 0.1 and 0.3%, i.e. 1 and 3 per 1000 procedures, respectively. The present results also confirm that in Finland second trimester TOP (i.e. during gestational Weeks 13–24) is mostly (95%) performed medically.

This nationwide retrospective cohort study gives information about the contemporary use of medical abortion in non-selected material. It was derived from a registry, the coverage of which is almost 100% (Gissler *et al.*, 1996). In addition, the hospital registry data for in-patient care, the provision of which is mandatory, was available from all hospitals and out-patient care data were available from all public hospitals, adding to the information value of the study. There were, however, differences in coding treatments (Nordic Centre for Classifications in Health Care, 2010) and diagnoses (International Statistical Classification of Diseases, 2010) among Finnish hospitals. Thus, the severity of reported adverse events may vary considerably. Moreover, while the registry differentiates between medical and surgical TOP, the database does not provide precise information on the medication used to perform TOP. We therefore restricted our analysis to years 2003–2006, during

Table II Adverse events and complications among women undergoing TOP between 2003 and 2006.

	First trimester (n = 17 087)	Second trimester (n = 1161)	OR (95% CI)	P-value	Adj. OR ^a	P-value
Adverse event						
1. Surgical evacuation (total)	1357 (7.9)	447 (38.5)	7.3 (6.4–8.3)	<0.001	7.8 (6.8–8.9)	<0.001
At the time of TOP	396 (2.3)	306 (26.4)	15.1 (12.8–17.8)	<0.001	15.2 (12.8–18.0)	<0.001
During follow-up	961 (5.6)	141 (12.1)	2.3 (1.9–2.8)	<0.001	2.5 (2.1–3.1)	<0.001
2. Haemorrhage (total)	2937 (17.2)	167 (14.4)	0.8 (0.7–0.96)	0.01	0.8 (0.7–0.98)	0.03
Haemorrhage with surgical evacuation	541 (3.2)	96 (8.3)	2.8 (2.2–3.5)	<0.001	3.1 (2.4–3.9)	<0.001
3. Infection (total)	330 (1.9)	46 (4.0)	2.1 (1.5–2.9)	<0.001	2.1 (1.5–2.9)	<0.001
Infection with surgical evacuation	138 (0.8)	28 (2.4)	3.0 (2.0–4.6)	<0.001	3.3 (2.2–5.0)	<0.001

Data are shown as n (%).

^aFirst trimester cohort was used as a reference adjusted for age, marital status, socio-economic status, previous deliveries and indication for TOP.

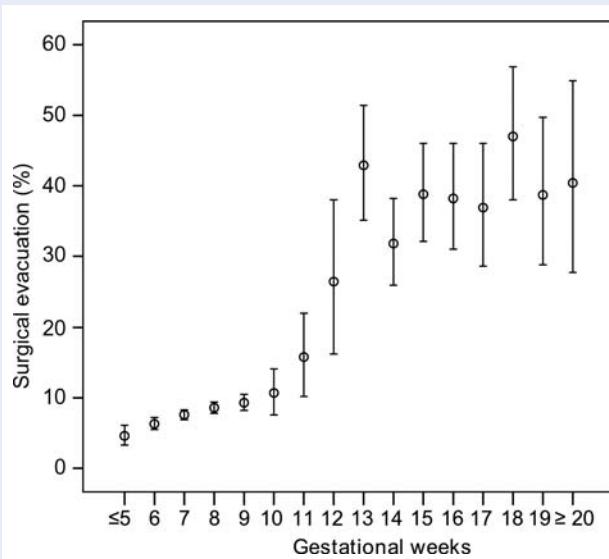


Figure 2 Percentage of surgical evacuation in relation to duration of gestation following medical TOP in 2003–2006. Bars represent 95% CI for percentage.

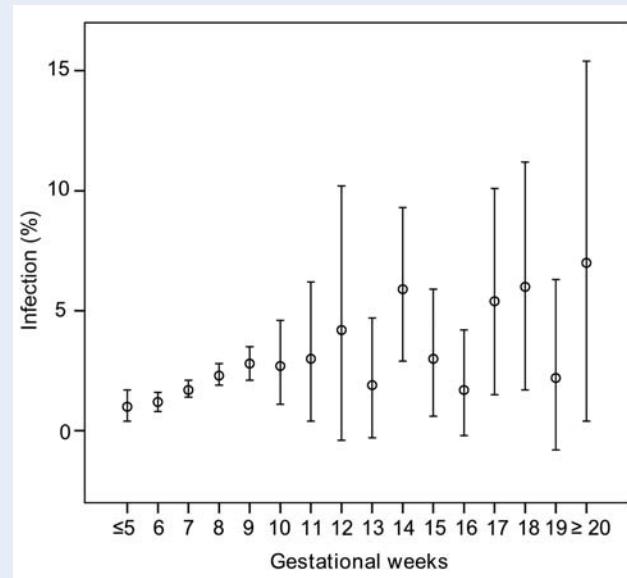


Figure 3 Percentage of infection in relation to duration of gestation following medical TOP in 2003–2006. Bars represent 95% CI for percentage.

which medical TOP using mifepristone and misoprostol was widespread throughout the country (THL, 2010a).

The rate of surgical evacuation associated with second trimester medical TOP was high (39%) in the present study. A potential explanation is that these data are derived from hospitals treating <200 second trimester terminations of pregnancy per year with all doctors performing the treatments. This may lead to unnecessary surgical treatments. Further, surgical evacuation of the uterus quickly after expulsion of the fetus was more or less routine until year 2000. For example, we published surgical evacuation percentages of 45–64% associated with second trimester medical TOP performed with mifepristone and misoprostol in 2001 (Heikinheimo *et al.*, 2004). Nevertheless, it will be interesting to see if the low rates in surgical

evacuation (8%: Ashok *et al.*, 2004) following medical second trimester TOP, reported from centres with extensive experience with medical methods, can also be reached at a national level.

Reassuringly, the incidence of infection leading to a hospital visit (4%) following medical second trimester TOP in this nationwide study was similar to that 3% reported earlier (Ashok *et al.*, 2004; Lohr *et al.*, 2008). Moreover, the risk of infection was largely associated with evacuation of residual tissue.

It is interesting to note that the incidence of reported haemorrhage was lower during the second trimester TOP when compared with that of the first trimester. However, if haemorrhage occurred, it resulted in surgical intervention in more than half of the cases during the second trimester and in less than one-fifth of the cases during the first trimester.

Also the need of surgical evacuation of residual tissue seemed to occur earlier following second than first trimester TOP. It may be speculated that the lower rate of haemorrhage seen after the second trimester TOP is due to the fact that these women are managed at the hospital and also undergo surgical evacuation more often. Thus, the lower incidence of reported haemorrhage following the second trimester TOP may be more due to different management than to a biological difference(s) between the first and second trimester TOP.

The optimal method for second trimester TOP continues to be debated, as medical second trimester TOP with mifepristone and misoprostol is associated with higher overall rate of adverse events and complications when compared with dilatation and evacuation (Grimes, 2008; Lohr et al., 2008). However, TOP performed with mifepristone and misoprostol during gestational Weeks 13–24 has been shown to be effective and acceptable (Ashok et al., 2004; Lohr et al., 2008). The safety of surgical TOP at more than 15 weeks of gestation depends on the skills of the practitioners (Grimes, 2008; Lohr et al., 2008). As the medical method for TOP is less dependent on the skills of doctors, it might be the preferred method in some health care settings.

We conclude that in comparison with medical TOP performed during the first trimester, medical second trimester TOP was associated with increased frequency of adverse events, most of which are minor. However, the risks of surgical evacuation or infection did not increase with increasing gestation duration in the second trimester. These data encourage further development and use of medical methods for second trimester TOP.

Authors' roles

All authors have equally participated in the planning of the study, analysis of the data and preparing of the manuscript.

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